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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,965	09/07/2006	Luisella Calabi	B358-US	4955

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EXAMINER	
GAKH, YELENA G	

ART UNIT	PAPER NUMBER
1797	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,965	CALABI ET AL.	
	Examiner	Art Unit	
	Yelena G. Gakh, Ph.D.	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment filed on 02/01/10 is acknowledged. Claims 2 and 13-14 are cancelled. Claims 1 and 3-12 are pending in the application and considered on merits.

Response to Amendment

2. In response to the amendment the examiner withdraws objections to the specification and claims and maintains all rejections established in the previous Office action, except for those for claims 2 and 13-14.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1 and 3-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a combination of specific shift reagents and endogenous or exogenous species, as well as nuclei, e.g. acetylsalicylic acid as the exogenous species and Dy-BOPTA as the shift reagent using ^{1}H MAS-NMR, does not reasonably provide enablement for method for all possible endogenous and exogenous species recited in the claims using all possible shift reagents recited in claims 10 and 11 and using MAS-NMR techniques with various nuclei. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. It would have been an undue experimentation for a practitioner in the art to perform the steps of claim 1 in order to perform the method of claim 1, i.e. "a) identify a set of possible SA candidates for said SA and nucleus combination, on the basis of the LIS produced on at least one NMR signal belonging to said exogenous or endogenous substance; b) identify a set of possible candidates for said SA, on the basis of the CC/s in which they distribute; and c) select said SA and nucleus combination, on the basis of the information gathered from steps (a) and (b)" with an infinite number of possible combinations for such sets, and especially taking into account the following excepts from the specification:

"The above MAS-NMR technique has been applied to the determination of the permeability of human blood cells by Magnetic Resonance Imaging Contrast Agents (MRI-CAs), particularly polyamino polycarboxylic Gd based contrast agents. This method comprises the use of a lanthanide complex able to produce a clearly detectable lanthanide induced shift (LIS) and a very weak relaxation (line broadening) on NMR signals of intra- and extra-cellular water protons. The rationale for this method relies on the complete isostructurality between the Gd-contrast agents (CA), which intra- or extra-cellular concentration has to be determined, and the lanthanide complex acting as shift agents (LIS agent). In other words, as both CA and LIS agent are supposed to show a very similar behavior (because of their isostructurality), the actual determinations of where the LIS agent is, i.e. its exact intra- or extra-cellular concentration, are deemed to substantially correspond to where the CA would be and to the CA intra- or extra-cellular concentration, respectively." (Page 5, lines 29-32, page 6, lines 1-9).

Furthermore,

"The use of a SA for cellular uptake measurements, in fact, is based on and may only be advantageously applied when the signals of interest, corresponding to the given EXO (or ENDO) in the intra- and extra- CCs, are both detectable and well separated, to allow a reliable measure of their areas wherein this means that no overlapping can exist. Moreover, the said signals must be due to the 100% of the EXO (or ENDO) in the sample. This means that the whole signal has to be completely detectable, "visible", with respect the spectrum base line." (Page 10, lines 6-12),

and

"In other words, in the method of the invention the presence of the SA may only determine a shift of the NMR signal of a substance when this same substance is very close to the SA, i.e. when both EXO and SA stay in the same cellular compartment. In this case, the measured LIS is a quantity directly linked to the absolute concentration of the analysed EXO in the different CCs, and its value is proportional to the ratio between the EXO and SA concentrations, hereinafter indicated as ρ^{EXO}=[SA]/[EX0]."

It appears that the condition for a successful output in performing the method, i.e.

"To identify the most suitable set of SAs and nuclei combination for the quantitative determination of the cellular uptake of a given EXO, the said EXO is dissolved in D_20 and, by employing a variety of combinations of different SAs with different nuclei and by varying the ratio ρ^{EXO} = [SA]/[EXO], LIS^{EXO} signals are thus measured.
SAs and nuclei combinations inducing the largest LIS^{EXO} signals are those most suitable for use with the EXO under investigation. Said largest LIS^{EXO} signal/s, hereinafter referred to as $marker^{EXO}$ signal/s, has/have to be considered as preferred according to the invention". (Page 13, lines 1-9).

will cause an undue experimentation for a practitioner in the art, since there are too many combinations of different nuclei, SA and ratios ρ^{EXO}. The specification does not appear to give any guidance to a routineer in the art, how such combinations should be searched. Furthermore, it is not apparent, as to how the best SA is chosen for a specific EXO/ENDO analyte under

investigation, which makes the scope of enabled method unclear. The situation is complicated by the following possibilities:

> "if EXO and SA distribute into more than one CC (as per Figures 3c-3h; 4c-4h), the possibility of determining all of the EXO compartmental concentrations may require additional stoichiometric calculations which complexity may vary for the different situations, depending from the availability of some or all of the CC volumes and the number of CCs where SA and EXO distribute. In any case, by means of LIS^{EXO} signal vs. ρ^{EXO} graph, the values of the EXO compartmental concentrations can be calculated. To sum up, step (3) of the method of the invention is carried out by taking into account the CC/s where EXO stay, the volume/s of said CC/s, the value/s of the area/s under the $marker^{EXO}$ signal/s, the calculated ρ^{EXO} for every CC in which EXO stays, and by solving the system of equations connecting these parameters." (Page 17, lines 13-24).

The only real Example 2 does not show, how Dy-BOPT was selected for acetylsalicylic acid (ASA) and whether this SA is known to be the best for ASA. Furthermore, ASA appears to be a very simple compound and is not exemplary for the possible analytes recited in the claims.

Claim Rejections - 35 USC § 102/103

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. **Claims 1, 3-7 and 10-12** are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Calabi et al. (J. Magn. Reson., 2002, IDS) (Calabi).

Calabi teaches "[a] new method, based on proton high-resolution magic-angle spinning (^{1}H HR-MAS) NMR spectroscopy, has been employed to study the cell uptake of magnetic resonance imaging contrast agents (MRI-CAs). The method was tested on human red blood cells (HRBC) and white blood cells (HWBC) (*Claim 12*) by using three gadolinium complexes, widely used in diagnostics, Gd-BOPTA, Gd-DTPA, and Gd-DOTA, and the analogous complexes obtained by replacing Gd(III) with Dy(III), Nd(III), and Tb(III) (*Claims 1, 3-7 and*

10-11) (i.e., complexes isostructural to the ones of gadolinium but acting as shift agents). The method is based on the evaluation of the magnetic effects, line broadening, or induced lanthanide shift (LIS) caused by these complexes on NMR signals of intra- and extracellular water." (Abstract). Thus, Calabi select three SA candidates and performs MAS-NMR spectroscopy to determine the compartmental concentration of said exogenous substance.

Response to Arguments

8. Applicant's arguments filed 02/01/10 have been fully considered but they are not persuasive.

Rejection under 112, first paragraph. The examiner respectfully disagrees with the Applicants' traverse of the rejection of pending claims under 112, first paragraph, scope of enablement. The examiner clearly demonstrated on the basis of the Applicants' own disclosure that performing the steps recited now in claim 1 in the scope of the claim would be an undue experimentation for any routineer in the art. Not only the disclosure specifically emphasizes applying polyamino polycarboxylic Gd based contrast agents as the most suitable for the performed method, but it also demonstrates that searching for isostructural exogenous and/or endogenous species to the contrast agent is the whole separate problem, to which the whole disclosure is devoted. While the idea underlying the method is clear and obvious for a person of ordinary skill in the art, its realization requires an undue experimentation. The required significant Applicants' effort which was both time and resource-consuming to come up with specific exogenous and/or endogenous species isostructurally corresponding to the contrast agents, specifically acetylsalicylic acid as an EXO species for Gd-BOPTA agent. The examiner considers this unfair to the practitioners in the art to make the same effort that the Applicants has made in order to come up with different combinations of the contrast agent and the EXO/ENDO species, besides the one found by the Applicants.

Rejection under 35 USC 102/103 over the prior art of Calabi. The examiner respectfully disagrees with the Applicants' traverse of the rejection of the pending claims over Calabi, since contrast agents and shift agents are both exogenous species for the cell. Furthermore, the only real example which was demonstrated in the specification for the uptake of EXO/ENDO species was related to acetylsalicylic acid, which is not "any molecule", for which uptake can be determined.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Vickie Y. Kim can be reached on (571) 272-0579. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

04/18/10

/Yelena G. Gakh/
Primary Examiner, Art Unit 1797